

Deformed Toric Ideal Constraints on Stoichiometric Networks

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ABSTRACT

We discuss chemical reaction networks and metabolic pathways based on stoichiometric network analysis, and introduce deformed toric ideal constraints by the algebraic geometrical approach. With the deformed toric ideal constraints, the shape of flux is constrained without introducing ad hoc constraints. To illustrate the effectiveness of such constraints, we discuss two examples of chemical reaction network and metabolic pathway; in the former the shape of flux is constrained completely by deformed toric ideal constraints, and in the latter, it is shown the deformed toric ideal constrains the parameters of flux at least partially.

Keywords: stoichiometric networks; deformed toric ideal constraints

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1 Introduction

The metabolic pathway analysis is one of the major fields in the systems biology and is the basis of the metabolic engineering and synthetic biology. With the development of experimental technology, this field is studied with practical objectives, such as clarifying the metabolic systems of life with biological interests and manufacturing biochemical products through metabolic processes.

In chemistry, it is important to identify the chemical mechanism. The instability of steady states of chemical reaction systems exhibits exotic dynamics, such as switching between multiple steady states, explosions, and sustained oscillations. The chemical reaction networks have been studied with the purpose of clarifying the chemical mechanism behind such phenomena.

Theoretical studies on chemical reaction networks are based on stoichiometric network analysis (SNA), which is the method based on the mass action kinetics. SNA was initiated by Clarke [1, 2, 3] and succeeded by Feinberg et al. [4, 5, 6, 7]. Gatermann et al. [8, 9, 10] have studied chemical reaction networks from the viewpoint of algebraic geometry, especially of polynomial rings. Inspired by their study, Shiu et al. have used toric varieties in the analysis [11, 12, 13]. There are also studies on bifurcations of dynamical systems with SNA [14, 15, 16, 17].

Metabolic pathways, on the other hand, have been studied by flux balance analysis (FBA) which introduces the steady state solution space, called ‘null space’ or ‘kernel space.’ The introduction of ‘elementary modes’ [18, 19, 20, 21, 22] and ‘extreme pathway’ [23] is specific progresses in this field. Review articles on these theme include refs. [24, 25]. For the discussions of these two approaches, see ref. [26].

This paper considers a unified approach to obtain constraints on the flux for both fields of chemical reaction networks and metabolic pathways, and applies SNA to analysis of metabolic pathways. While the theoretical analysis in these two fields have common bases, the steady state solutions have been analyzed in different ways, and there have been few works discussing them in a unified way. Ref. [23] is an exception, where the relationships be-

tween SNA and FBA are discussed, but they do not apply SNA to analyze the metabolic pathways. We discuss algebraic geometrical constraints on stoichiometric networks: from the monomial vector expression of flux, we derive the deformed toric ideal, that works as constraints on the parameters of the flux. The existence of such constraints had not been pointed out before.

We show two examples of analysis by the proposed method in a chemical reaction network and a metabolic pathway. In the former example, we show that all of flux parameters are determined completely by the reaction coefficients with the deformed toric ideal constraints. In the latter, we show that the flux parameters are partially constrained by the deformed toric ideal, without which the flux parameters cannot be restricted. We also describe the relation between the deformed toric ideal constraints and thermodynamic feasibility.

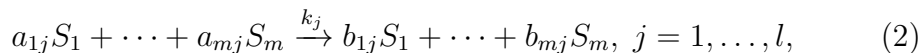
This paper is organized as follows. In section 2, we review the basic formulation of stoichiometric network analysis with an example of chemical reaction network. In section 3, we explain stoichiometric flux. In section 4, we discuss deformed toric ideal constraints. In section 5, we apply the arguments of SNA and deformed toric ideal constraint to an example of metabolic pathways. In section 6, we give the conclusions of the analysis of the current paper and the future directions of mathematical studies of stoichiometric networks.

2 Stoichiometric Network Analysis

The stoichiometric network analysis (SNA) starts with the chemical reaction systems which are described by

$$\dot{x} = N \cdot v(x; k). \quad (1)$$

Here, x and \dot{x} are a concentration vector of reactant species and its time derivative, respectively, N is the stoichiometric matrix, and $v(x; k)$ is the flux vector, where k is reaction coefficients. The stoichiometric matrix, explained below, can be determined, once we know the form of chemical equations,



where k_j is the reaction coefficient for reaction j . The form of flux vector $v(x; k)$ is determined by the mass action kinetics. By the mass action kinetics, the verocity of reaction is described by

$$k_j[S_1]^{a_{1j}} \cdots [S_m]^{a_{mj}}, \quad (3)$$

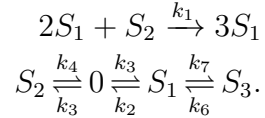
where $[S_i]$ denotes the concentration of S_i . With the matrices A and B of the elements a_{ij} and b_{ij} , respectively, N is defined as

$$N = B - A \quad (4)$$

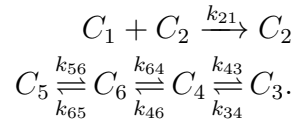
The stoichiometric equation (1) shows that the time derivative of concentrations of reactant species is represented by the product of the stoichiometric matrix and flux vector.

Example 2.1(Gatermann et. al. 2005 [14])

We consider the phosphofructokinase reaction which is a part of glycolysis. It is an extension of a reaction system proposed by Sel'kov '68 [27]. There are $m = 3$ chemical species; S_1 denotes the product Fructose-1,6-biphosphate, S_2 denotes the reactant Fructose-6-phosphate and the extension S_3 stands for another intermediate in equilibrium with Fructose-6-phosphate. The $l = 7$ reaction laws are given by



We arrange the left and right hand side of reaction laws (2) in so-called *complexes* C_j , $j = 1, \dots, n$ with the rate constants $k_{ij} > 0$;



By the mass action kinetics, this reaction system is described by the following differential equations,

$$\begin{aligned} \dot{x}_1 &= k_{21}x_1^2x_2 + k_{46} - k_{64}x_1 - k_{34}x_1 + k_{43}x_3, \\ \dot{x}_2 &= -k_{21}x_1^2x_2 + k_{56} - k_{65}x_2, \\ \dot{x}_3 &= k_{34}x_1 - k_{43}x_3. \end{aligned}$$

Represented by the stoichiometric equation form, N and $v(x; k)$ in eq.(1) are given by

$$N = \begin{pmatrix} 1 & 1 & -1 & 0 & 0 & -1 & 1 \\ -1 & 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix} \quad (5)$$

and

$$v(x; k) = \begin{pmatrix} k_{21}x_1^2x_2 \\ k_{46} \\ k_{64}x_1 \\ k_{56} \\ k_{65}x_2 \\ k_{34}x_1 \\ k_{43}x_3 \end{pmatrix}. \quad (6)$$

3 Stoichiometric Flux

The steady state solution for a chemical reaction (dynamical) system is defined by the concentrations whose time derivatives vanish ($\dot{x} = 0$), i.e.

$$Nv(x; k) \equiv Nz = 0, \quad (7)$$

where $z \equiv v(x; k)$. When there is no confusion, we use z hereafter. The solution of z that satisfies eq.(7) forms a convex polyhedral cone, and the steady state solution space is called ‘kernel space’ or ‘null space.’ Minimal generating vectors of the steady state solution are called ‘extreme currents.’ Each extreme current is the generator of a convex polyhedral cone. A non-negative linear combination of the extreme currents is also a steady state solution.

Example 2.1(continued)

The extreme currents satisfying eq.(7) are given by

$$E_1 = \begin{pmatrix} 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, E_2 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 0 \end{pmatrix}, E_3 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \end{pmatrix}, E_4 = \begin{pmatrix} 1 \\ 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \quad (8)$$

If we take the linear combination of the extreme currents,

$$z = j_1 E_1 + j_2 E_2 + j_3 E_3 + j_4 E_4 \quad (9)$$

$$= \begin{pmatrix} j_4 \\ j_1 \\ j_1 + j_4 \\ j_2 + j_4 \\ j_2 \\ j_3 \\ j_3 \end{pmatrix}, \quad (10)$$

where, j_l are nonnegative linear combination coefficients. Thus, z is a general steady state solution of eq.(7). While the coefficient j_l might look to take an arbitrary nonnegative value, they have some constraints as will be shown in the next section.

4 Deformed Toric Ideal Constraints on Stoichiometric Network

By the explicit monomial vector form, the steady state solution forms a deformed toric ideal. This can be seen by describing the elements of z as monomials in the original x coordinates (in affine space). The ideal $I_{Y_L}^{def} = \{f \in \mathbb{Q}[z] | f(x) \equiv 0\} \subseteq \mathbb{Q}[z]$ is called a deformed toric ideal, where Y_L is the configuration whose entries are the exponents of the monomials in the flux vector.

We will see that the form of flux is constrained by the deformed toric ideal. For the mathematical basics, see refs. [28, 29] and for the derivation of toric ideals, see ref. [30].

Example 2.1(continued)

For the current example, the generators of the deformed toric ideal are obtained as a binomial form, and it is easy to calculate from eq.(6);

$$I_z = \langle z_2 - k_{46}, k_{21}z_5z_3^2 - k_{64}^2k_{65}z_1, k_{34}z_3 - k_{64}z_6, z_4 - k_{56} \rangle. \quad (11)$$

By the correspondence between the elements of vector z in the representation by z_l and by j_l , the deformed toric ideal can be described by j_l coordinates. By substituting (10) with (11), we obtain deformed toric ideal in j_l coordinates.

$$I_j = \langle j_1 - k_{46}, k_{21}j_2(j_1 + j_4)^2 - k_{64}^2k_{65}j_4, k_{64}j_3 - k_{34}(j_1 + j_4), j_2 + j_4 - k_{56} \rangle \quad (12)$$

In the rest of this section, we show that j_l are constrained by the deformed toric ideal. As a result, j_l are determined without introducing ad hoc constraints. Note that in the following derivation we use only the generators of deformed toric ideal, that is, the relationships between monomials. This has not been used in any previous studies on this example. From the constraints that each generators of deformed toric ideal are zero, we obtain the following expressions of j_l ,

$$\begin{aligned} j_1 &= k_{46}, \\ j_2 &= -Z + k_{56}, \\ j_3 &= k_{34}(k_{46} + Z)/k_{64}, \\ j_4 &= Z. \end{aligned} \quad (13)$$

Here, Z is the solution of the following 3-dimensional algebraic equation,

$$\begin{aligned} &k_{21}Z^3 + (-k_{21}k_{56} + 2k_{21}k_{46})Z^2 \\ &+ (k_{21}k_{46}^2 + k_{64}^2k_{65} - 2k_{21}k_{46}k_{56})Z - k_{21}k_{46}^2k_{56} = 0. \end{aligned} \quad (14)$$

The positivity conditions for j_l give

$$0 < Z < k_{56}. \quad (15)$$

Eq.(13) shows that the linear coefficients j_l depend on the value of reaction rates k_{ij} and Z . Eq.(14) shows that Z also depends on the value of k_{ij} , and thus j_l depends on the value of k_{ij} , which means j_l cannot be chosen arbitrarily, indifferent to the value of k_{ij} . Note that these constraints are derived by the algebraic property of monomials, without introducing any ad hoc constraints. This strong constraint seen in the current example does not hold for general reactions: the example has many generators in the deformed toric ideal enough to constrain all j_l by k_{ij} . In general cases, j_l are only partially constrained by k_{ij} .

Substituting j_1, \dots, j_4 of eqs.(13) for eq.(10), we obtain the stoichiometric flux z under deformed toric ideal constraints,

$$z = \begin{pmatrix} Z \\ k_{46} \\ k_{46} + Z \\ k_{56} \\ -Z + k_{56} \\ k_{34}(k_{46} + Z)/k_{64} \\ k_{34}(k_{46} + Z)/k_{64} \end{pmatrix}. \quad (16)$$

This means that we can determine the form of flux (length of extreme currents), once we know the value of reaction coefficients k_{ij} by means of experimental observation.

5 Example of Metabolic pathway

In the above sections, we considered a chemical reaction network as an example. The same argument holds for metabolic pathways. In this section, we consider deformed toric ideal constraints with a concrete example of metabolic pathway.

Example 5.1:

Feedback Inhibition of pathway, Palsson (2011) [31]

We use this example because it is one of the simplest realistic pathways whose monomial vector form of the flux is explicitly known.

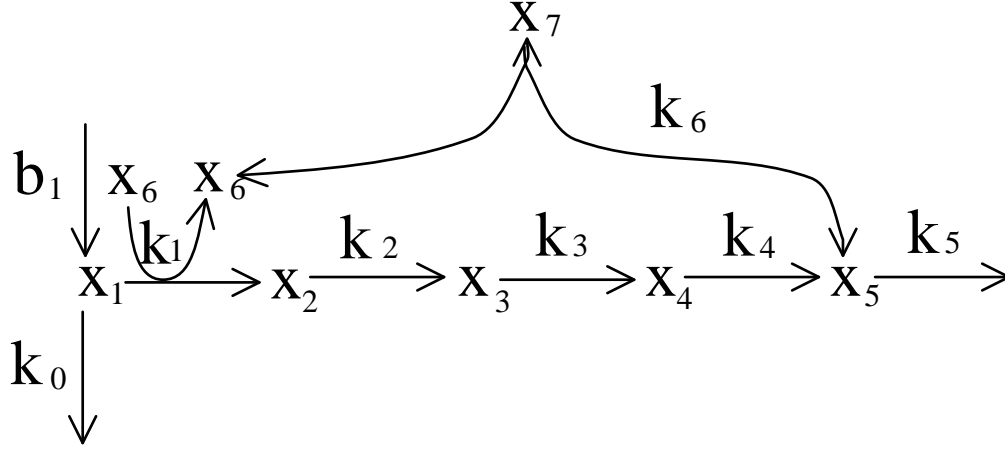


Figure 1: Feedback Inhibition of pathway

In a biosynthetic pathway, the first reaction is often inhibited by the end product of the pathway. Fig.1 illustrates a prototypical feedback loop in a biosynthetic pathway.

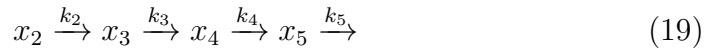
A metabolic intermediate x_1 is formed and degraded as



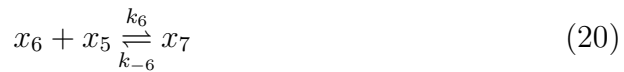
Then, if an enzyme x_6 is expressed, x_1 can be converted to x_2 :



which is followed by a series of reactions



to form x_5 , the end product of the pathway. The end product has inhibitory feedback to the enzyme x_6 by binding to it and converting it into an inactive form:



This system represents a simple negative feedback loop. The differential equations that describe this feedback loop are

$$\dot{x}_1 = b_1 - k_0x_1 - k_1x_6x_1, \quad (21)$$

$$\dot{x}_2 = k_1x_6x_1 - k_2x_2, \quad (22)$$

$$\dot{x}_3 = k_2x_2 - k_3x_3, \quad (23)$$

$$\dot{x}_4 = k_3x_3 - k_4x_4, \quad (24)$$

$$\dot{x}_5 = k_4x_4 - k_5x_5 - (k_6x_5x_6 - k_{-6}x_7), \quad (25)$$

$$\dot{x}_6 = -k_6x_5x_6 + k_{-6}x_7, \quad (26)$$

$$\dot{x}_7 = k_6x_5x_6 - k_{-6}x_7. \quad (27)$$

In the above equations, RHS is the sum of reaction rates. In ref.[31] (chapter 2.2), reaction rates are described mathematically using kinetic theory. He discusses mass action kinetics as one of the fundamental concept of kinetic theory.

We analyze this pathway with SNA, which was not done in ref. [31]. In the stoichiometric matrix form, these differential equations are written as

$$\dot{x} = Nz, \quad (28)$$

and the metabolic pathway analysis starts with the following equation,

$$Nz = 0. \quad (29)$$

The LHS is the product of the stoichiometric matrix and the flux vector, and we will find the steady state solution. This is the flux balance equation. For flux balance analysis (FBA), see refs. [32, 33], for example.

For the current example, the stoichiometric matrix is

$$N = \begin{pmatrix} -1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 0 & 1 & -1 & 1 & 0 \\ 0 & -1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & -1 & 0 \end{pmatrix}, \quad (30)$$

and the flux vector is

$$z = \begin{pmatrix} k_1 x_6 x_1 \\ k_6 x_5 x_6 \\ k_0 x_1 \\ k_2 x_2 \\ k_3 x_3 \\ k_4 x_4 \\ k_5 x_5 \\ k_{-6} x_7 \\ b_1 \end{pmatrix}. \quad (31)$$

For the metabolic pathway analysis, extreme currents correspond to extreme pathways [23]. The extreme pathways computed from the stoichiometric matrix are

$$E_1 = \begin{pmatrix} 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \end{pmatrix}, E_2 = \begin{pmatrix} 1 \\ 0 \\ -1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 0 \\ 0 \end{pmatrix}, E_3 = \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}. \quad (32)$$

By taking a linear combination of the extreme pathways with nonnegative coefficients, the metabolic flux is obtained;

$$\begin{aligned} z &= j_1 E_1 + j_2 E_2 + j_3 E_3 \\ &= \begin{pmatrix} j_2 \\ j_1 + j_3 \\ j_1 - j_2 \\ j_2 \\ j_2 \\ j_2 \\ j_2 \\ j_1 + j_3 \\ j_1 \end{pmatrix}. \end{aligned} \quad (33)$$

Here, we derive the deformed toric ideal of this pathway. Admitting Laurent monomials, from the monomial vector representation of z , the deformed toric ideal is given by

$$I_z = \langle z_1 k_6 k_0 / z_3 - z_2 k_1 k_5 / z_7 \rangle. \quad (34)$$

From the corresponding representation of flux, the deformed toric ideal represented by j_l is given by

$$I_j = \langle j_2 k_6 k_0 / (j_1 - j_2) - (j_1 + j_3) k_1 k_5 / j_2 \rangle. \quad (35)$$

There is only one deformed toric ideal constraint, which is obtained by equating the generator to zero. This is a relation between the extreme pathways. The parameter region is partially constrained by the reaction coefficients. In metabolic pathways, the shape of flux (length of extreme pathway) is important. The shape of flux is partially constrained by experimental observations, furthermore automatically constrained by the deformed toric ideal constraints.

In the above example, there is only one deformed toric ideal constraint. Comparing with the example of chemical reaction network, the number of constraints is small. This is caused by the small number of the generators of the deformed toric ideal. The smallness originates in the limited number of species which appear as the same form in the chemical equations.

The points of $j_1 = j_2$, $j_2 = 0$ or $j_1 + j_3 = 0$ are critical points between the thermodynamically feasible and infeasible region in the sense of refs. [34, 35], where thermodynamic feasibility is described as the orthogonality to the cycles of the oriented matroid associated with stoichiometric matrix N . At the above points, the elements of flux is zero. For the detail, see ref. [36].

In the rest, we will show that, in addition to the steady state equations and mass balance, which were already known in ref. [31], the above deformed toric ideal constraint provides the complete solution to the steady state of this system. First, as in [31], the steady state equations are given by

$$0 = b_1 - k_0x_1 - k_1x_6x_1, \quad (36)$$

$$0 = k_1x_6x_1 - k_2x_2, \quad (37)$$

$$0 = k_2x_2 - k_3x_3, \quad (38)$$

$$0 = k_3x_3 - k_4x_4, \quad (39)$$

$$0 = k_4x_4 - k_5x_5 - (k_6x_5x_6 - k_{-6}x_7), \quad (40)$$

$$0 = -k_6x_5x_6 + k_{-6}x_7, \quad (41)$$

$$0 = k_6x_5x_6 - k_{-6}x_7. \quad (42)$$

It is known that these equations can be combined to give a quadratic equation,

$$y^2 + ay - b = 0, \quad (43)$$

where

$$y = k_2x_2, a = k_5k_{-6}(1 + k_1e_t/k_0)/k_6, b = k_5k_{-6}k_1e_tb_1/(k_6k_0), \quad (44)$$

that has one positive root in y . Note that from $y = k_2x_2 = z_4 = j_2$ the variable j_2 is given by a positive root of eq.(43). Next, the sum of x_6 and x_7 gives us the mass balance in the enzyme:

$$x_6 + x_7 = e_t, \quad (45)$$

where e_t is the total amount of enzyme (constant).

In ref. [31], these constraints are not studied with j_l coordinates. With the representation of flux by the extreme pathways, eq.(45) can be represented by j_l coordinates, eq.(45) gives

$$(j_1 + j_3)k_5/j_2k_6 + (j_1 + j_3)/k_{-6} = e_t. \quad (46)$$

With these conditions, the region taken by the parameters j_l is further limited, combined with the deformed toric ideal constraint and nonnegativity

conditions on j_l .

$$j_1 = j_2(k_6k_0 + k_1k_5)/k_1k_5, \quad (47)$$

$$j_3 = \frac{j_2\{k_5k_{-6}(e_ik_1k_6 - k_1k_5 - k_6k_0) - j_2(k_1k_5k_6 + k_6^2k_0)\}}{k_1k_5(k_5k_{-6} + j_2k_6)} \geq 0. \quad (48)$$

Since from eq.(43) j_2 is determined uniquely, eq.(47) shows j_1 is also unique. In addition, when the RHS of eq.(48) is nonnegative, a unique solution for (j_1, j_2, j_3) is determined, and when the RHS is negative, there is no steady state solution.

6 Conclusions

In this paper, we considered deformed toric ideal constraints on stoichiometric networks, treating the chemical reaction networks and metabolic pathways in a unified way. This paper is the first that pointed out that the deformed toric ideal constrains the parameters of flux. We clarified that even the shape of flux is constrained by the deformed toric ideal.

In general, for metabolic pathways, reactants and products are so diverse that chemical species may not appear as the same form in the LHS and RHS of the chemical equations. The number of generators for the deformed toric ideal is thus small and the effect of constraints may be limited. By considering sub-networks of large scale metabolic pathways, however, they should be more influential. It will be interesting to consider sub-networks like ATP production in energetic metabolism, because there appear some chemical species as the same form in the LHS and RHS of the chemical equations.

In refs. [34, 35], thermodynamic constraints are considered explicitly, in terms of the non-equilibrium thermodynamic systems. Such constraints are not discussed in the current paper, but the study with thermodynamic constraints, added to the deformed toric ideal constraints, will be interesting. By considering these constraints, flux is constrained in another form.

As another topic, which is pointed out for the example of chemical reaction network, flux forms a convex polyhedral cone. The algebraic geometrical

study, using commutative algebra and combinatorics, will also be interesting. This is within our future work.

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